Exhibit D

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 4 Cases*	

EXPERT REPORT OF NICOLE B. FLEISCHMANN, M.D.

In re PELVIC MESH/GYNECARE LITIGATION,	SUPERIOR COURT OF NEW JERSEY LAW DIVISION – BERGEN COUNTY MASTER DOCKET NO. BER-L-11575-14 CIVIL ACTION In Re Pelvic Mesh/Gynecare Litigation Case No. 291

EXPERT REPORT OF NICOLE B. FLEISCHMANN, M.D.

(Gynecare TVT/TVT-O)

I have prepared this Expert Report in the matter of In re: Pelvic Mesh/Gynecare, Master Docket No. BER-L-11575-14 pending in the Superior Court of New Jersey, Bergen County.

My opinions set forth in this report are made to a reasonable degree of medical probability, and are based on information and knowledge I have acquired from my research and review of medical literature, personal experience in private practice, education, training, teaching, and discussion and interaction with other pelvic surgeons in professional activities and conferences. I reserve the right to amend this report or my opinions as I review additional information.

QUALIFICATIONS

I am a practicing urologist with subspecialty training in Female Pelvic Medicine and Reconstructive Surgery (FPMRS). I have board certification both in Urology and in FPMRS, a new board certification with the American Board of Urology (ABU) and the American Board of

OB/GYN (ABOG). Following my graduation from medical school and my residencies in surgery and in urology, I completed a fellowship in Female Urology and Voiding Dysfunction at the New York University School of Medicine. Since my fellowship, I have had a busy clinical practice at Westchester Urological Associates, a division of Advanced Urology in White Plains, New York, where I treat almost exclusively women with urologic issues such as incontinence, pelvic organ prolapse, recurrent urinary tract infections, hematuria and kidney stones. In addition to my private practice at White Plains Hospital, I am very involved in the training of residents (Urology and Gynecology) and fellows through my responsibilities as the Associate Fellowship Director of FPMRS and Associate Clinical Professor of Urology and Ob/Gyn at Albert Einstein College of Medicine in Bronx, NY. I run a clinic, didactic sessions and perform surgery at the teaching hospital once a week. My credentials are further set forth in my *curriculum vitae*, which is Exhibit A to this Report.

On a daily basis, I diagnose and treat women with urinary incontinence, a debilitating condition which affects millions of women around the world. I take great pleasure in working to eliminate this problem for women and improving their overall quality of life, through both surgical and non-surgical treatment. For at least two or three days of the week, I perform and train others to perform surgical procedures to correct stress urinary incontinence. The most common procedure that I do is the midurethral sling. Over the years, I have placed roughly 1500 slings, the overwhelming majority of which are the Gynecare TVT in both retropubic and obturator (TVT-O) approaches. In addition, I perform other types of anti-incontinence procedures such as autologous fascial slings and Burch colposuspensions on a routine basis. I also do many procedures for pelvic organ prolapse including transvaginal mesh repairs and

robotic sacral colpopexy using Y-mesh. I used Prolift and Prolift +M when they were on the market.

MATERIALS I HAVE REVIEWED

In the course of preparing this report, I have reviewed numerous documents. I have examined the published literature on TVT and TVT-O. I have reviewed professional education materials produced by Ethicon, as well as the Instructions for Use (IFU) of the Gynecare TVT and TVT Obturator. I have also read the numerous medical society statements and the statement issued by the Food and Drug Administration (FDA) regarding synthetic midurethral slings. I have also read numerous company documents. A list of the materials I have reviewed in formulating my opinions is attached as Exhibit B to this report and will be updated as I review more materials.

URINARY INCONTINENCE

Urinary incontinence (UI), a debilitating medical condition that affects millions of women, is defined as the involuntary loss of urine. According to Nygaard et al (Jama, 2008) approximately 15.7% of women suffer from urinary incontinence or 12 million US adults. One study (Wu, et al. 2009 JOBGYN) forecasts that as the population ages, by 2050 there will be a public health crisis with over 48 million American women affected. The annual direct cost of urinary incontinence in the United States (in 1995 dollars) was estimated as $16.3 billion (Wilson et al. Obstet Gynecol. 2001).

Urinary incontinence has both a physical and emotional impact on a woman's quality of life. Physical complications include skin problems such as skin infections and sores from constantly wet skin as well as recurrent urinary tract infections. UI can affect one's overall

physical health by impairing the ability to exercise or be generally active for fear of increasing leakage episodes. Because UI may cause social isolation, loss of sexual function, and other psychosocial problems, it could have significant impact on patients' emotional well-being and sense of personal dignity. Studies have shown that patients suffering with UI are more depressed, psychologically distressed, emotionally disturbed and socially isolated. (Zorn et al. JUROL 1999.) Moreover, compared with continent individuals, those patients with UI also have higher levels of anxiety, lower quality of life scores, and poorer life satisfaction (Melvile, 2002 Am. J. Obstet. Gynecology). As a result, urinary incontinence has an adverse effect on patients' daily lives, which can be devastating in the more extreme cases, and can become a barrier for normal social function.

Types of Urinary Incontinence

Urinary incontinence is divided into two subtypes: stress urinary incontinence (SUI) and urge urinary incontinence (UUI). People who have both subtypes have mixed urinary incontinence (MUI). SUI is defined as urine loss during periods of activity such as coughing, sneezing, lifting and exercise. The mechanism of urine loss is either weakened tissue support to the opening of the bladder (urethral hypermobility) or deficiency of the closure mechanism that holds urine inside the bladder (intrinsic sphincter deficiency), resulting in leakage of urine during periods of physical stress to the bladder. The amount of leakage can vary from a few drops to a significant volume. The most common reason for someone to have SUI is after a vaginal delivery, but other risk factors such as smoking, aging and genetics can all play a role.

Urge urinary incontinence is the involuntary loss of urine which is accompanied by or preceded by a strong urge. It is the inability to defer urinating in order to make it to the

bathroom. The volume of urine loss can be large, causing extreme embarrassment. This condition can affect people of all ages, but is most common in the postmenopausal woman. Certain neurologic conditions such as cerebral vascular accidents, Parkinson's disease and multiple sclerosis can result in UUI. Another condition which leads to UUI is bladder outlet obstruction, which is when the bladder becomes irritated because it is unable to empty freely such as in the case of men with enlarged prostates. As previously stated, people who have symptoms of both UUI and SUI are said to have mixed urinary incontinence, but typically, one of the subtypes is the prevailing problem.

Diagnosis of Incontinence

The treatments for UUI and SUI are different, so it is important that the clinician comes to the correct diagnosis before initiating a therapy. Most physicians will use a variety of tools to assess the type of incontinence. The first step is to acquire an accurate and thorough history from the patient. This can be accomplished through filling out questionnaires and an interview. Most women will be able to describe the circumstances in which they leak, and this is an invaluable piece of information to the clinician. It is also helpful to identify other medical conditions the patient suffers from, medications she takes, previous surgeries she has undergone, and family history. In the course of the interview, the physician should learn about the everyday life of the patient: what she does for a living, what her personal life is like, especially with regards to sexual activity, as all this information can be helpful when diagnosing and formulating a treatment plan.

The physical examination is also crucial to diagnosing the type of incontinence. In many cases, urine leakage can be elicited in women with SUI by simply asking them to cough or bear

down during a pelvic examination. In addition, it is important to note any defects in the vaginal wall that may coexist with urinary incontinence such as cystocele, rectocele or uterine prolapse. Prolapse is a condition in which the pelvic organs herniate into the vagina and may or may not be accompanied by urinary incontinence. Other helpful information includes a post void residual test (PVR) in which the amount of urine left behind after a woman urinates is measured either by sonogram or catheter drainage. A urinalysis and urine culture determines when a urinary tract infection is present or when there is the presence of blood in the urine, which may indicate another problem such as bladder cancer. When indicated, clinicians may ask patients to keep a voiding diary to log the amount they drink, how often they urinate and how many leakage episodes they have in a 24 hour period.

Urodynamic testing can be an extremely helpful tool in diagnosing incontinence conditions. It is a procedure by which the physician is able to demonstrate the exact cause of incontinence by reproducing the episode in a controlled setting. The test involves placing a small catheter in the bladder and another in the rectum or vagina. The catheter monitors pressure as the bladder fills with water. The physician is able to assess the capacity of the bladder, whether there are any involuntary bladder contractions during the filling process, whether the patient leaks with a cough and at what volume and pressure, and whether the voiding episode is normal and unobstructed. In some cases, the physician will look inside the bladder with cystoscopy to assess whether there are any abnormalities which could cause urine leakage such as a bladder stone or foreign body.

Treatment of Urge Urinary Incontinence

If the etiology of the incontinence is determined to be urgency incontinence, a conservative approach is usually offered in the form of behavioral management. Monitoring quantity and quality of fluid ingested, decreasing bladder irritants such as coffee and alcohol, performing kegels or pelvic floor exercises, and practicing timed voiding (going to the bathroom by the clock instead of waiting to the urge to arise) all fall under this category. Behavior therapy can be very useful in mild forms of incontinence, but tends to be less effective as symptoms become more severe.

A helpful adjunct to behavioral therapy in OAB is medication. The most common drugs available are anti-muscarinics which decrease unwanted urge symptoms and increase the functional bladder capacity. Currently available medications in this category are oxybutynin (Ditropan), tolteridine (Detrol), trospium (Sanctura), solifenicin (Vesicare), darifecinin (Enablex), Gelnique and the Oxytrol patch. The most common side effects of this class of medication are dry mouth, constipation, blurry vision and reflux. In 2012, mirabegron (Myrbetriq) was approved for use in overactive bladder – with a different mechanism of action and side effect profile.

Second line treatments for urge incontinence or overactive bladder are offered when medications are not effective or the side effects make them intolerable. BOTOX® (onabotulinumtoxinA) intravesical injection was recently FDA approved for both neurogenic and idiopathic overactive bladder. InterStim therapy or sacral nerve modulation is an implantable device which delivers a continuous low level electrical impulse to the nerves of the pelvis to help

with bladder control. Both of these procedures can be performed either in the office or the operating room under local anesthesia.

As with any procedure, even minimally invasive overactive bladder procedures have risks of complications. The most common side effects of BOTOX® include UTIs (3.6% to 54.5% with four of the RCTs reporting rates of >40.0%), urinary retention (10 studies and ranged from 0% to 43%), the need to perform self-catheterization (20 studies and ranged from 0% to 43% with six studies reporting rates higher than 20.0%, with the need for self-catheterization persisting for 6-9 months in some patients), and neurological adverse events (AUA/SUFU 2014 OAB Guidelines). Complications with InterStim therapy or sacral nerve modulation include pain at the stimulator site (3.3 to 19.8% of patients), pain at the lead site (4.5 to 19.1% of patients), lead migration (2.2 to 8.6% of patients), infection/irritation (2.2 to 14.30% of patients), electric shock (5.5 to 10.2% of patients) and the need for surgical revision (6.25 to 39.5% of patients, with greater than 30% of patients in most studies) (AUA/SUFU 2014 OAB Guidelines).

Treatment of Stress Urinary Incontinence

Stress urinary incontinence differs from urge incontinence in that it is often more effectively managed with surgical procedures than medications. There are no FDA approved medications that are indicated for the treatment of stress urinary incontinence. Over the years, a variety of surgical techniques have been adopted, each with varying success and complication rates. A very recent study estimates that the lifetime risk of surgery to treat SUI (or POP) in women is 20% by age 80. (Wu et al., Obstet. Gyn., June 14, 2014).

Since Arnold Kegel first described pelvic floor exercises over 50 year ago, "Kegels", as they are known, have been a mainstay treatment for stress incontinence. Pelvic floor muscle

therapy is the process by which someone learns to relax and contract the levator ani or pelvic floor muscles in order to strengthen them. In some cases, the doctor will use biofeedback or electric stimulation to the pelvic floor in order to help the patient better identify these muscles.

Extensive research has been done on the efficacy of pelvic floor exercises, both with and without biofeedback therapy. Many studies have shown that if the woman is diligent, compliant and determined, exercise therapy improves leakage symptoms, as high as 50% in some studies (Berghmans LC et. al., Br. J. Urol, 1998). But as with any exercise program, successful outcomes require long-term motivation and this is difficult for many people to maintain. There is little doubt that in cases of mild SUI, pelvic floor exercises should be tried. However, there is question whether they are effective for women with more severe leakage symptoms. A recent study in the New England Journal of Medicine (Labrie et al., N. Engl. J. Med. 2013) showed that when women with moderate to severe SUI were randomized to treatment groups for pelvic floor therapy or surgery (midurethral sling insertion), the sling arm had much higher subjective cure (85% vs. 53%) and improvement rates (91% vs. 64.4%).

The use of a bulking agent/injectable is the most minimally invasive procedure for stress incontinence. The clinician will inject a substance underneath the lining of the urethra, usually in an office setting, which causes the lumen of the urethra to tighten and make the bladder less leaky. Agents which have been commonly used are collagen, Coaptite, Durasphere and Macroplastique. Although this is a minimally invasive technique with a low complication rate, the results are often disappointing (25-50% cure or improvement) and the effect is temporary (under 12 months requiring multiple repeat injections). (Gorton E, et al., Periurethral collagen injection: a long-term follow-up study, BJU Int. 1999 Dec; 84(9):966-71.).

A number of surgical procedures have evolved over decades for the treatment of SUI in women. The following section of my report seeks to describe the primary procedures that physicians have used and to consider their relative risks and benefits. At trial, I may present the various surgical treatment options to the jury, which may involve the use of photographs, diagrams, illustrations, surgical tools, animations, videos or any of the documents referenced on Exhibit B to this report.

Retropubic suspensions are open procedures which use permanent suture (i.e. Prolene, Gortex, Ethabond) material to attach the endopelvic fascia at the neck of the bladder to the back of the pubic bone or ligament. Traditional Burch colposuspension is a standard approach which requires a wide abdominal incision and is often performed during abdominal surgeries such as hysterectomy and sacrocolpopexy, a surgical procedure used to repair pelvic organ prolapse. The Marshall-Marchetti-Krantz (MMK) is a similar procedure which also requires a wide abdominal incision. Both procedures require a prolonged hospital stay and recovery period. Some newer less invasive procedures use laparoscopy and robotics, which requires small "keyhole" incisions. Laparoscopy has a faster recovery time and less postoperative pain than the open Burch, but its long-term effectiveness is not yet known. Hong, J.H. et al., Long Term Results of Laparascopic Burch Colposuspension for Stress Urinary Incontinence in Women, J. Korean Med Sci. 2009 Dec; 24(6):1182-6.

Research has shown that while open retropubic suspensions are effective treatments for stress urinary incontinence (Lapitan MC, Cody JD. et al. published in the Cochrane database , 2012), in general, there is greater morbidity than more minimally invasive approaches. In addition, there is a greater chance of postoperative de novo pelvic organ prolapse than after slings.

Sling procedures were first introduced in the early 1900s and have undergone multiple modifications since that time. Von Giordano has been credited with performing the first pubovaginal sling operation in 1907. High quality trials have shown as good if not better success rates for the pubovaginal sling procedure when compared to Burch colposuspension. (Albo, M et. al., NEJM 2007; Bandarian, M. et. al., J. Obstet. Gynaecol. 2011; Novara, et al. Eur. Urol. Aug. 2010). The conventional pubovaginal sling procedure involves making a wide incision above the pubic bone to harvest a layer of tissue from the abdominal wall (rectus fascia). Alternatively, a strip of fascia from the outer thigh (fascia lata) is used. Permanent sutures (either Prolene or Ethabond) are sutured to either side or the graft. This tissue strip is set aside and later serves as the sling that is implanted through an incision in the vaginal wall. In this respect, the fascial sling is like two surgeries instead of one, because it requires first the harvesting and then the implantation. The vaginal incision to implant the fascial sling is much larger than what is required for a midurethral sling. In most cases, the entire anterior vaginal wall is undermined, approximately 5 or 6 cm in length in an "upside down U" configuration. This is considerably more extensive a dissection than the approximately 1 to 1.5 cm incision that is needed to implant TVT or TVT-O. (See TVT and TVT-O IFUs.) The piece of tissue is passed under the urethra and bladder neck, somewhat like a hammock, and secured above the abdominal wall by tying the permanent suture to itself. The sling works by compressing and supporting the urethra without being too tense, which can cause urinary obstruction.

As is the case with retropubic suspensions, the autologous fascial sling procedure has the disadvantage of high morbidity with prolonged hospital stay (2-3 days) and often, the need for prolonged postoperative catherization. A randomized controlled study known as the SISTEr trial (Albo, ME et al. NEJM 2007) was a landmark paper comparing retropubic suspensions (Burch

colposuspension) to pubovaginal sling (autologous fascia). A total of 655 women were randomly assigned to study groups: 326 to undergo the fascial sling procedure and 329 to undergo the Burch procedure. At 24 months, stress incontinence specific success rates were higher for women who underwent the fascial sling procedure than for those who underwent the Burch procedure (66% vs. 49%, P<0.001). However, more women who underwent the fascial sling procedure had urinary tract infections, difficulty voiding, and postoperative urge incontinence. There are also complications from the harvest site such as seromas, infections/abscesses and incisional hernias. (Latini JM et al., Efficacy and morbidity of autologous fascia lata sling cystourethropexy. J. Urol. 2004;171:1180–4.) Bladder herniation has also been infrequently reported. (Gomelsky and Dmchowski, Incisional Bladder Hernia after Rectus Fascial Sling, J. Urol., June 2003: Vol. 169, Issue 6, Page 2299.)

In order to reduce operative time, recovery time and overall morbidity of the pubovaginal sling procedure, several modifications have evolved which have strived to either eliminate the fascial harvest and/or eliminate the suprapubic incision. Allograft or cadaveric fascia has been used to replace the woman's own tissues. Short term outcomes are similar to autologous fascia, but some studies suggest late failures and histological studies may be a cause for concern for durability. (O'Rielly & Govier, J. Urol. 167:1356, 2002.) Furthermore, little is known about the graft–host relationship and possible mechanisms of graft degradation for cadaveric materials (Woodruff A.J., et al., Urology, 2008.) The risks of disease transmission with these materials remain unknown. Traces of genetic material have been isolated from commercially available cadaveric sling materials although there have been no reports of disease transmission related to cadaveric grafts in the urologic literature.

Over the years, physicians have continued to pursue new surgical treatments to combat stress incontinence. The transvaginal bone anchored sling had also been adopted using allograft or xenograft (animal product) with far worse results then the retropubic sling, and has been abandoned. The Raz/Stamey and modified Peyrera needle suspension urethropexies were developed in the early 1990s as minimally invasive procedures for stress incontinence with low morbidity but poor long term outcomes and have since been abandoned.

The bottom line is that, prior to TVT, in order to better her quality of life, a woman had to commit herself to a morbid procedure requiring days of hospitalization and a long convalescence period. It is not surprising that many women who lead active lives would decline surgical correction of their incontinence because of the difficulty fitting it into their lives. The introduction of minimally invasive midurethral slings has prompted many more women to treat their incontinence. (Oliphant SS et al., Trends Over Time With Commonly Performed Obstetric and Gynecologic Inpatient Procedures, J. Obstet. Gynecol. 2010;116(4):926; Jonsson Funk M. et al, Trends in the surgical management of stress urinary incontinence, J. Obstet Gynecol. 2012;119(4):845.).)

The Evolution of the Gynecare TVT Sling

Gynecare TVT Tension-Free Support for Incontinence ("TVT"), the first minimally invasive sling to utilize non-absorbable polypropylene (Ethicon, Somerville, NJ, USA) was introduced to the market in Europe in 1997 and in the U.S. in 1998. TVT revolutionized the treatment of SUI by offering effective and long term management of women's leakage, with results similar to or better than the old standards (Burch and autologous fascial sling), but without significant morbidity. The procedure was originally described by Ulmsten and Petros in

1995 and was based on the 'Integral Theory' whereby reinforcing the pubo-coccygeal muscles at the level of the mid-urethra corrects the deficient mechanism that causes incontinence. The sling material, PROLENE® mesh, is a synthetic macroporous (>75 microns), polypropylene monofilament knitted mesh (Amid type 1) placed by a retropubic approach. The original sling procedure was described as appropriate in an outpatient setting under local, light general or regional anesthesia. The mesh implant was mechanically cut, which is still offered today. The mechanically cut mesh induces an initial "Velcro effect" and then tissue ingrowth to anchor in the host tissues within 3–4 weeks after insertion. The use of a permanent, non-absorbable mesh increases the durability of the repair and reduces the chances that urethral support will weaken over time.

TVT has now been on the market for 18 years and is taught in residencies and fellowships as a matter of course because it is widely recognized as a gold standard treatment option for SUI in a broad category of women. Following the introduction of the original TVT, there have been numerous iterations of the TVT sling addressing surgeon's differing preferences based on various considerations: patient factors, surgeon training and personal experience. In 2006, Ethicon began to offer a version of TVT Retropubic that employed a laser-cut mesh implant.

The Gynecare TVT Obturator sling

The obturator technique to implant a sling was developed to bypass the retropubic needle passes which increase the possibility of bladder injury and retropubic hematoma. The outside- in obturator technique (Delorme, 2004) involves passing helical shaped trocars from the inner thigh region around the inferior pubic rami from a point just lateral to the insertion of the adductor

muscle at the level of the clitoris. The trocars exit through the vaginal wall incision lateral to the urethra on either side and a finger is placed under the vaginal wall to guide the trocar into place. The mesh is then connected to the trocars and they are backed out through the thigh, allowing the tape to lie flat under the urethra. The products initially employing this approach were Monarch (AMS) and ObTape (Mentor).

By 2003, Professor Jean de Leval of the University of Liege, Belgium, had developed the inside-out technique of the obturator approach, which reversed the direction of the trocar passage. In this procedure, the points where the helical passers will exit at the skin level are identified by tracing a horizontal line at the level of the urethra meatus. The exit points are located 2 centimeters above this line and 2 centimeters outside the thigh crease. After minimal para-urethral sub-vaginal dissection of 1 cm, the right obturator membrane is perforated with the tips of the scissors, which are then slightly opened. The Winged Guide is then pushed through the obturator membrane. The device is gently slipped along the gutter of the Winged Guide so as to pass through the obturator foramen. The Winged Guide is then removed and the passer is rotated around the inferior pubic ramus at a 45 degree angle, exiting the thigh at the predetermined location. The tube is pulled from the supporting passer, which is removed by a backwards-rotational. The process is repeated on the contralateral side. The sling is tensioned appropriately and the plastic sheaths are removed. Ideally, cystoscopy should be performed after the case, but it is not required. The product employing this technique is the Gynecare TVT-O (Ethicon). The mesh implant used in TVT-O is identical in composition and construction to the extensively studied polypropylene implant in TVT Retropubic. Thus its safety profile when it was launched in 2004 was in part built on the seven year history of the use of the same implant in the global market. In addition, in its pre-launch medical assessments of TVT-O, Ethicon

considered thousands of reported cases of the use of outside-in obturator slings, as well as Dr. de Leval's initial feasibility study on 107 patients implanted using the inside-out procedure. (2003 Clinical Expert Report for TVT-O by Dr. M. Weisberg.).

The TVT-O is often my "go to" procedure to treat a patient's SUI for several reasons. First and foremost, it is safe. In my hands, the intraoperative and postoperative complication rate is negligible. Second, it works well. Objective and subjective continence rates in my practice are as good as any other procedure I may do. I prefer the inside-out technique of the TVT-O to the outside-in technique because of the minimal dissection required. In order to pass the trocar from outside to in, the surgeon needs to make a dissection big enough to admit a finger which guides the trocar past the urethra. In the inside-out approach of TVT-O, no finger dissection is necessary to safely pass the guide or the trocar. Minimal dissection helps to ensure that the sling remains where it is placed at the midurethra where it has maximum effect. In addition, there is a risk when pushing a finger into the small dissection required for a outside-in approach to rip the vaginal wall creating a larger vaginal incision that is less easy to close. The fact that the incision site for TVT-O stays small minimizes the risk for mesh exposure at the incision site.

I have used Gynecare TVT and TVT-O for years and have been fortunate to have started my training during a time when these products were available. I cannot imagine what my practice would be like if I could not offer women such safe and effective options to treat a debilitating condition such as stress incontinence. My mentors have talked about what the treatment was like "back in the day." I treat patients who still recall the debilitating surgery they had 30 years ago which kept them in the hospital for a full week and they could not urinate for three months after. It is such a different experience for my patients, most of whom cannot

believe what a positive experience it was and wish they had done it 10 years earlier. They have no idea what their predecessors had to endure.

Medical Literature on Gynecare TVT and TVT Obturator

In formulating my opinions in this report, I have performed an extensive review of the peer-reviewed medical literature studying TVT, TVT Obturator, and synthetic mid urethral slings in general. While my extensive surgical experience, training, teaching and other professional interactions with my colleagues obviously provide me with an important knowledge based about these devices, my review of the literature is critical to my opinions. The literature on TVT and TVTO is important because it tracks the progress of thousands and thousands of women who have been implanted with these PROLENE slings over the past 20 years, and under often rigorous trial protocols, and under the scrutiny of peer reviewers. Many of the studies are meta-analyses and randomized controlled trials, which are considered Level 1 evidence according to the Oxford pyramid of evidence which ranks scientific evidence in terms of its weight and reliability. In addition, several of the studies that I have reviewed and discuss below follow TVT or TVT-O patients over five or ten years, providing important long term data about the functioning of these devices.

There has been an extraordinary amount of scientific research conducted on the midurethral sling: a Medline literature search reveals over 2000 publications. There over 100 randomized controlled studies and abstracts supporting the use of Gynecare TVT. (ETH.MESH.08307644 and 45.) The clinical history of Gynecare TVT is critical to the history of Gynecare TVT-O, which uses the same mesh sling in the same indication, but through a different surgical approach. The first long-term data on Gynecare TVT was published by

Nilsson et al., who reported objective and subjective cure rates of 84.7% with a median follow-up of 56 months. Subsequently, Nilsson et al. reported longer follow-up (11 years) in a prospective observational cohort of 90 women. They showed a 90% objective and 77% subjective cure rate with no long-term adverse events. The seventeen year data published in August 2013 was similar indicating that TVT Retropubic is a time-tested and safe procedure to restore continence to women.

Long term data has been published in several other series. In 2008, Liapis et al. confirmed Nilsson's results in a study of 70 women who underwent TVT and were followed for 7 years. Objective cure was 80% as measured by urodynamic parameters and pad testing. Olsson et al. studied one hundred and forty-seven women with stress incontinence that underwent TVT sling implants. At eleven and one half years, the objective cure rate was 84%. The subjective cure rate was 77%, while 18% had improved. Ninety-four percent of the patients were satisfied with the surgical result. No late adverse effects of the operation were found. Additional long term studies with similar results are Groutz, et al, 2011, Aigmueller et al. 2011 (10 years follow up), Heinonen, et al 2012 (10.5 years follow up), Serati, et al 2012 (10 years follow up), Svenningsen et al. 2013 (10.75 years follow up), and Khan ZA et al, (abstract) June 2014 (10 year, 73% success rate).

The inventor of Gynecare TVT-O, Professor Jean de Leval, and his colleague David Waltregny, both from the University of Liege, Belgium, have generated a substantial body of published literature on the TVT-O device. Following an initial feasibility study on 107 patients, Prof. de Leval in 2003 initiated a prospective, observational trial of Gynecare TVT-O on 102 patients, who represented only a portion of the patients in whom they had implanted the device. (Waltregny et al., J. Urology, Vol. 175, 2191-95 (2006)). 99 of the 102 patients presented for 1

year follow up, of which 91% of patients reported complete cure of SUI symptoms. Four patients required tape release or section for voiding difficulties, and de novo voiding difficulties were reported by 7% of the patients. No patient had vaginal wall erosion at the one year follow up.

Three-year minimum follow-up (median, 40 mo) was available for 91 of the 102 original patients (89.2%). No erosion or persistent pain was noted. Disappearance and improvement of SUI were observed in 88.4% and 9.3% of the patients, respectively. These cure rates were similar to those obtained 1 yr after the operation. No patient presented symptoms suggestive of vaginal, bladder, or urethral erosion, neurologic complication, or persistent pain. Waltregny D, et al (Eur Urol. 2008 Feb;53(2):401-8. Epub 2007 Aug 21.02). Professors de Leval and Waltregny also performed cadaveric studies with Prof. Pierre Bonnet to study the anatomic considerations associated with the obturator route. (Bonnet, P. et al., J. Urology 2005.) In 2007, Professors de Leval and Waltregny published the three-year follow up on 810 patients who had received TVT-O at their hospital in Liege, Belgium since 2002, reporting cure rates of almost 90% at 3-year minimum follow up. de Leval et al., Rev. Med. Liege 2007: Synthese 2007:86-94 (French language).

Since the development of the procedure to implant TVT-O in 2003 by Professor de Leval, other surgeons throughout the world have published a significant volume of clinical studies demonstrating the safety and effectiveness of the device. Serati et al. (Eur Urol. 2013 May; 63(5):872-8) evaluated the efficacy and safety of TVT-O implantation for management of pure SUI in 191 women with a follow up of five years. The five-year subjective and objective cure rates were 90.3% and 90.8%, respectively. These five year findings were reproduced by Cheng et al. (2012). A more recent study by Athanasiou et al. (2013) followed 124 consecutive

women with TVT-O implants for seven years and noted objective and subjective cure rates of 81.5 % (101/124) and 83.5 % (103/124), respectively.

TVT v. TVT-O

Numerous studies which have compared the TVT Retropubic and Obturator approaches and have shown little difference in success rates as far as 5 years out. Angioli et al (Eur Urology 2010) performed a randomized controlled study and concluded that at five years, both surgical techniques are safe, with similar results: 72.9% and 71 % of patients objectively cured after TVT-O and TVT Retropubic, respectively. At the International Continence Society meeting 2011, Laurikainen et al. presented the results of a 5 year multicenter prospective comparison and showed 88 % of the TVT and 93 % of the TVT-O patients were completely satisfied with the operation. In both groups, 96% would definitely recommend the operation to a friend. (Laurikainen et al. abstract, *Retropubic TVT Compared with Transobturator TVT (TVT-O) in Treatment of Stress Urinary Incontinence: Five year Results of a Randomized Trial.*) Similar findings have been shown by other investigators (Krofta et al Int Urogynecol J (2010) 21:141–148). Zhu et al. performed a meta-analysis of 20 randomized controlled studies and a pooled estimate of effectiveness and complications was made. Objective and subjective cure was comparable with the two techniques. Complication rates varied with relative risks with 95% confidence intervals for pooled effects under the fixed effects model were: 0.20 (0.09 - 0.45), for bladder injury, 0.37 (0.16 - 0.86) for hematoma, and 2.35 (1.57 - 3.51) for postoperative pain, suggesting an 80% risk reduction of bladder injury, 63% risk reduction of hematoma, and a 1.35% risk elevation for postoperative pain with TVT-O. There was no significant difference between complications of urinary tract infection 1.14 (0.78 - 1.65), lower urinary tract symptoms 1.60 (0.67 - 3.79), recatheterization 0.93 (0.59 - 1.44), and tape erosion 0.90 (0.48 - 1.67).

A landmark study presented by The Urinary Incontinence Treatment Network in the NEJM entitled Retropubic versus Transobturator Midurethral Slings for Stress Incontinence (Richter et al. 2010), also known as the TOMUS trial, was a multicenter, randomized equivalence trial comparing outcomes with retropubic and transobturator midurethral slings in women with stress incontinence. The patients in the retropubic arm were treated with TVT Retropubic and the patients were in the obturator arm were treated with TVT Obturator or AMS's Monarc sling. A total of 597 women were randomly assigned to a study group. At one year follow up, the rates of objectively assessed treatment success were 80.8% in the retropubic-sling group and 77.7% in the trans-obturator sling group. Subjective success was lower in both groups (62.2% and 55.8% respectively). Rates of patient satisfaction were 85.9% for the retropubic group verses 90% for the transobturator group. The rates of voiding dysfunction requiring surgery (sling lysis or removal) were 2.7% in those who received retropubic slings and 0% in those who received transobturator slings (P = 0.004), and the respective rates of neurologic symptoms were 4.0% and 9.4% (P = 0.01). There were no significant differences between groups in postoperative urge incontinence, satisfaction with the results of the procedure, or quality of life. The group concluded that the one-year objective rate of success for both procedures were equivalent with a slightly different complication profile which was acceptably low.

In the two-year follow up to the TOMUS trial (Albo, ME et al. J Urol 2012), the investigators assessed the frequency of complications such as urinary tract infection, voiding dysfunction and wound complications requiring and not requiring surgical intervention. Of 597 randomized participants, 516 (86.4%) were assessed. Objective success rates for retropubic and transobturator mid urethral slings were 77.3% and 72.3%, respectively and subjective success

rates were 55.7% and 48.3%, respectively. Patient satisfaction was 86.3% for the retropubic approach and 88.1% for the transobturator approach. Frequency of de novo urgency incontinence (retropubic 0% vs transobturator 0.3%) and occurrence of mesh exposure (retropubic 4.4% vs transobturator 2.7%) were not significantly different. The retropubic mid urethral sling group had higher rates of voiding dysfunction requiring surgery (3.0% vs 0%,) and urinary tract infections (17.1% vs 10.7%), whereas the transobturator group had more neurological symptoms (9.7% vs 5.4%). The authors noted that although the rates of objective and subjective cure rates had decreased modestly from the one year follow up, "study participants from both surgical groups reported a high level of satisfaction as well as improvements in urinary symptom severity and QOL [quality of life] 24 months after surgery."

Five year follow up on the TOMUS trial suggested a slight decrease in success for both retropubic and transobturator slings, however, satisfaction remained high in both arms. Women undergoing a transobturator sling procedure reported more sustained improvement in urinary symptoms and sexual function. New mesh erosions occurred in both arms over time, although at a similarly low rate. Women in the retropubic arm had a slightly increased rate of voiding dysfunction (urinary urgency) and a greater negative impact on quality of life as compared to those who had the obturator approach. (Kenton et al., J. Urol 2015.)

Interestingly, these same authors were involved in the SISTEr trial comparing these same parameters in both Burch colposuspension and pubovaginal sling. The data suggests a lower or equivalent incidence for all these categories in the retropubic and transobturator midurethral sling groups. Postoperative UTI has an incidence of 17.1% (n=52) in the TVT group and 10.7% in the transobturator group compared to 32% (n=105) and 43% (n=157) in the Burch and PVS groups. Postoperative voiding dysfunction is 3% (n=9) in the TVT group, 0% in the

transobturator group, and 0% and 6.1% (n=20) in the Burch and PVS groups. There were 11 wound related complications requiring intervention and 6 not requiring intervention in the TVT group. These numbers compare favorably to 13 surgical and 69 nonsurgical complications in the Burch group; and 11 surgical and 71 non-surgically managed wound complications in the pubovaginal sling group. The Urinary Incontinence Treatment Network also performed a 2 year follow up on this cohort of women and found that with regards to sexual function, there was improvement after TVT and TVT-O. (Zyczynski, H. et al. Am. J. OBGYN 2012.)

Laurikainen et al (2014) presented a 5 year multicenter trial which compared –TVT retropubic to TVT-O. The objective cure rate was 84.7% in the TVT group and 86.2% in the TVT-O group, with no statistical difference between the groups. Subjective treatment satisfaction was 94.2% in the TVT group and 91.7% in the TVT-O group, with no difference between groups. Complication rates were low, with no difference between groups. Athanasiou et al (2014) performed a 7 year retrospective study on TVT-O. They reported overall objective and subjective cure rates of 81.5 % (101/124) and 83.5 % (103/124), respectively.

Some studies have suggested that when urethral hypermobility is the underlying cause of stress incontinence, the 2 techniques show equal efficacy but when intrinsic sphincter deficiency (defined as low leak point pressure under 60m H20) is the cause, there may be an advantage to the TVT Retropubic (Araco et al, 2008; Karateke et al. 2009, Rechberger et al Eur. Urology 2009)). Interestingly, the TOMUS trial did not reproduce this finding and noted an equal success rate regardless of leak point pressure. Again, in these cases the subject of sling tensioning is paramount. It is the surgeon's judgment which dictates each individual patients' needs.

Meta-Analyses

The original Cochrane review on midurethral slings (Ogah, J., et al., Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women (Review) Copyright © 2010 The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd.), which included sixty-two trials involving 7,101 women, concluded the following:

- minimally invasive synthetic suburethral sling operations appear to be as effective as traditional suburethral slings (8 trials, n=599, risk ratio (RR) 1.03, 95% confidence interval (CI) 0.94-1.13), but with shorter operating time and less postoperative voiding dysfunction and de novo urgency symptoms;
- minimally invasive synthetic suburethral sling operations appear to be as effective as open retropubic colposuspension (subjective cure rate at 12 months RR 0.96, 95% CI: 0.90-1.03; at 5 years RR 0.91, 95% CI: 0.74-1.12) with fewer perioperative complications, less postoperative voiding dysfunction, shorter operative time, and hospital stay;
- minimally invasive synthetic suburethral sling operations have significantly less de novo urgency and urgency incontinence, shorter operating time, hospital stay, and time to return to daily activities; a retropubic bottom-to-top route is more effective than top-to-bottom route (RR 1.10, 95% CI: 1.01-1.20; RR 1.06, 95% CI: 1.01-1.11) and incurs less voiding dysfunction, bladder perforations, and tape erosions.
- Monofilament tapes such as TVT and TVT-O have significantly higher objective cure rates (RR 1.15, 95% CI: 1.02-1.30) compared to multifilament tapes and fewer tape erosions (1.3% vs. 6% RR 0.25, 95% CI: 0.06-1.00).

- The obturator route had a lower objective cure than the retropubic route (84% vs. 88%; RR 0.96, 95% CI: 0.93-0.99; 17 trials, n=2,434), although there was no difference in subjective cure rates. However, there was less voiding dysfunction, blood loss, bladder perforation (0.3% vs. 5.5%, RR 0.14, 95% CI: 0.07-0.26), and shorter operating time with the obturator route.

The Cochrane Review compared the rates of several potential complications such as bladder perforation, de novo urgency and perioperative complications such as hematoma formation. The incidence of post-operative pelvic pain or dyspareunia was not demonstrated with any significant degree of frequency throughout the trials. The authors concluded that the current evidence base suggests that minimally invasive synthetic suburethral slings are as effective as traditional slings and open retropubic colposuspension, but with fewer postoperative complications.

In an update to the original Cochrane Review, released in 2015, the authors analyzed 81 trials that evaluated 12,113 women. Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. *Cochrane Database of Systematic Reviews* 2015, Issue 7. Art. No.: CD006375. DOI: 10.1002/ 14651858.CD006375.pub3. (July 1, 2015)

The results were:

- Subjective cure rates between transobturator tapes passed using a medial-to-lateral (TVT-O) as opposed to a lateral-to-medial (Monarch) approach were similar (RR 1.00, 95% CI 0.96 to 1.06; 6 trials, 759 women; moderate quality evidence, and RR 1.06, 95%CI 0.91 to 1.23; 2 trials, 235 women; moderate quality evidence).

- There was moderate quality evidence that voiding dysfunction was more frequent in the medial-to-lateral group (RR 1.74, 95% CI 1.06 to 2.88; 8 trials, 1121 women; moderate quality evidence), but vaginal perforation was less frequent in the medial-to-lateral route (RR 0.25, 95% CI 0.12 to 0.53; 3 trials, 541 women).

The 81 trials, which included 12,113 patients through June 2014, demonstrated that "over 80% of women with stress urinary incontinence are cured, or have significant improvement in their symptoms, with either operation [retropubic or obturator sling], for up to five years after surgery…. [T]he information that is available for quality of life shows that it improves as a result of these operations, though there is no clear difference between the two procedures." (Ford 2015.)

The authors further concluded that "mid-urethral sling operations have been the most extensively researched surgical treatment for stress urinary incontinence (SUI) in women and have a good safety profile. Irrespective of the routes traversed, they are highly effective in the short and medium term and accruing evidence demonstrates their effectiveness in the long term. This review illustrates their positive impact on improving the quality of life of women with SUI. With the exception of groin pain, fewer adverse events occur with employment of a transobturator approach. When comparing transobturator techniques of a medial-to-lateral versus a lateral-to-medial insertion, there is no evidence to support the use of one approach over the other." (Ford 2015.)

In addressing the potential risks of midurethral slings, the authors stated that "tapes passing behind the pubic bone (retropubic) seem to carry a greater risk of injuring the bladder during the operation and of women experiencing problems emptying their bladder completely

after surgery. However, this operation leads to less groin pain in the short term. There is some limited evidence that this way of inserting the tape has a lower risk of requiring a repeat operation in the long term compared to tapes passing through the groin (transobturator). There is moderate quality evidence that overall reported rates of tape-related complications are low, such as erosion of the tape into the vagina at about 2% for both routes of tape insertion. The reported occurrence of problems with sexual intercourse including pain was low, and leakage of urine during intercourse are improved." (Ford 2015, at 30.) Ultimately the authors found that "women's outcome for quality of life and sexual function improved significantly after all surgical approaches" of mid urethral sling. (Id. at 47.)

Tommaselli performed a meta-analysis of medium and long term data on synthetic slings. (Tommaselli et al., Int'l Urog. J., published online May 20, 2015.) There were 11 RCTs [14–24] and 38 nonrandomized studies, including prospective, retrospective, and cohort studies [25–62] with a total of 6,406 patients. The authors looked at objective and subjective cure rates as well as long term complications. Retropubic midurethral slings (RP-MUS) had similar objective cure rates (OR 1.15, 95 % CI 0.75 – 1.76) but higher subjective cure rates than transobturator midurethral slings (TO-MUS) (OR 1.76, 95 % CI 1.08 – 2.86), although one study found similar subjective cure rates as between RP-MUS and TVT-O specifically (OR 0.92, 95% CI 0.47-1.80). Bladder injuries were more frequent (OR 7.01, 95 % CI 2.94 – 17.90) and vaginal erosions were less frequent for RP-MUS (OR 0.24, 95 % CI 0.07 – 0.84). Pain-related complications were more common with TO-MUS than with minimally invasive tapes (OR 8.75; 95 % CI 9.02 – 5). The authors concluded that "RPMUS and TO-MUS have similar objective cure rates in the long-term and medium-term but TOTs have a lower subjective cure rate than TVT. This efficacy is

backed by a high safety profile, and by a limited number of complications which were seldom severe."

Schimpf et al. performed a large meta-analysis on all treatments of female stress incontinence and concluded the following: "For women considering retropubic or transobturator midurethral sling, we recommend either intervention for objective and subjective cure and that decision be based on which adverse events are of greatest concern to patient:"

- Retropubic slings result in lower rates of sling erosion, need to return to operating room for treatment of sling erosion, groin/leg pain, and vaginal perforation.
- Transobturator midurethral slings result in shorter operative time, fewer bladder/urethral perforations, less perioperative pain, fewer urinary tract infections, and less overactive bladder symptoms.

In my own practice of over 1500 slings, most of which are Gynecare TVT or TVT-O slings, I can corroborate the findings of these studies. I use Gynecare TVT-O because I feel it is safe with a high success rate. With proper tensioning techniques, there is an acceptably high cure for stress incontinence with an acceptably low need for post-operative sling adjustment procedures (loosening or lysis). Postoperative de novo urgency is a known risk but exists with any surgery to treat SUI. Bladder injury is a reportable event. Urethral injury is rare but easily recognized and repaired as it is directly in the surgical field. Groin pain is self-limited, usually resolves in the first 24 to 48 hours. I rarely see persistent groin pain beyond four to 6 weeks.

TVT-O (Inside out) v. TOT (Outside In)

Certain of Plaintiffs' experts assert that outside-in obturator procedures are safer than TVT-O because of the nature of the passage and the helical trocars. I disagree with this opinion

because the peer reviewed medical literature, including randomized controlled trials and meta-analyses, simply do not support this conclusion.

For example, Tan, P.F. et al. conducted a meta-analyses which looked at 10 randomized controlled trials comparing TVT-O with TOT (outside in obturator approach), studying over 700 patients. Tan P.F. et al., Effectiveness and Complication rates of tension-free vaginal tape, transobturator tape, and tension free vaginal tape-obturator in the treatment of female stress urinary incontinence in a medium to long term follow up, Meta-analysis of randomized controlled trials, Saudi Med. J. 2014; Vol. 35(1). The authors reported subjective cure rates of 80.9% for TVTO and 81.7% for TOT (no statistically significant difference). The objective cure rates were 89.6% in TVTO and 89.3% for TOT, again with no statistically significant difference. With regard to complication rates, low complication rates were reported in all included studies, but the authors reported that "the reoperation rate was significantly higher in TOT…compared with TVTO" but there was no significant difference in vaginal erosion (exposure), groin/thigh pain, voiding difficulties/urinary retention and de novo urgency. Further sensitivity analysis of only "high quality RCTs" showed a significantly lower vaginal exposure rate with TVTO. (Id., Figure 4.).

Latthe et al. also performed a meta-analysis that included 4 trials that directly compared TVTO and TOT. Latthe, P. et al., Two routes of transobturator tape procedures in stress urinary incontinence: a meta-analysis with direct and indirect comparison of randomized trials, 2009 BJU Int'l; 106:68-76. The authors reported equivalent results for subjective and objective cure at six months. (Table 1.) There was a slightly higher risk of UTI in the TVTO group but this was not statistically significant. On indirect comparison, the risk of bladder injury, and voiding

difficulties as lower in the TVTO group, and the risk of de novo urgency was similar among the two groups.

In the 2015 Cochrane Review, Ford et al. reported on 10 trials studying 1199 women which demonstrated no statistically significant differences in subjective cure rates. Regarding complications, vaginal perforations were "significantly less likely to occur with the medial to lateral approach" (TVTO), and voiding dysfunction happened significantly more in the medial to lateral approach. There were no statistically significant differences among the two groups in terms of overall perioperative complication rate, major vascular/visceral injuries, bladder perforation, de novo urgency and urge incontinence, detrusor overactivity, vaginal tape erosions and groin/thigh pain. (Ford et. al. 2015).

The Gold Standard

Numerous investigators and societies have concluded – and I agree – that the synthetic midurethral sling via either a retropubic or transobturator approach is the gold-standard treatment for women with stress incontinence based on, among other reasons, large meta-analyses of the data showing equal/better outcomes and decreased morbidity compared to older procedures. (Cox, et al. Nature Reviews, 2013; Novara et al. Europ. Urol. 2010).

In 2009, a panel of experts developed the American Urological Association (AUA) guidelines for the urologist treating stress incontinence in the "index patient" – the otherwise healthy female who elects surgical correction for her stress incontinence. The guidelines were based on a total of 436 articles which were suitable for inclusion in the meta–analysis. They looked at outcomes and complications for multiple types of anti-incontinence procedures. In this exhaustive analysis, it was shown that complications are possible in any given procedure. The

complications associated with slings of any type are bladder perforation, voiding dysfunction and UTI. In the case of TVT, there is an added complication of mesh exposure. The panel agreed that this is the only complication that is unique to the midurethral sling procedure.

Their conclusions were as follows:

1. In this meta–analysis, the midurethral slings had an efficacy comparable to autologous slings in the surgical treatment of SUI.
2. Several "versions" of the midurethral sling procedures do not have similar long–term efficacy data.
3. There are complications that may occur that are unique to specific mesh materials; however, these complications appear to be infrequent. Intraoperative use of cystoscopy can be performed to minimize the risk of urinary tract injury or erosion.
4. The midurethral sling is an alternative in the management of SUI. The incidence and implications of these complications along with the more rapid recovery and more efficient return to normal voiding after surgery should be discussed with patients before surgery.

   (Dmochowski,R J Urol. 2010 May;183(5):1906-14. doi: 10.1016/j.juro.2010.02.2369. Epub 2010 Mar 29.Update of AUA guideline on the surgical management of female stress urinary incontinence .)

The AUA released a Position Statement in November 2011 on the use of vaginal mesh for the surgical treatment of SUI. The statement noted that the efficacy of synthetic polypropylene mesh slings is equivalent or superior to other surgical techniques, based on Level 1 evidence, with a follow-up to 10 years, and these are not associated with a significant increase in adverse events. The AUA agreed with the FDA recommendation included in its 2008 Public Health Notification of including a comprehensive informed consent before synthetic sling surgery, disclosing all possible risks and adverse events. Additional recommendations included not only rigorous urological training in pelvic anatomy and pelvic surgery, and intraoperative cystoscopy to exclude urinary tract injury, but specific surgical expertise on 'specific sling

techniques' as well as the diagnosis and treatment of related complications. The statement concluded that 'synthetic slings are an appropriate treatment choice of women with stress incontinence, with similar efficacy but less morbidity than conventional nonmesh techniques'.

In January 2014, the American Urogynecological Society (AUGS) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) released a joint position statement on the use of polypropylene mesh midurethral slings. These nationally and internationally recognized societies are comprised of leaders in the fields of both urology and gynecology, with subspecialty training in FPMRS. Their position statement stated, among other things, that:

1. Polypropylene material is safe and effective as a surgical implant.

2. The monofilament polypropylene mesh MUS is the most extensively studied antiincontinence procedure in history.

3. Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for our patients.

4. The FDA has clearly stated that the polypropylene MUS is safe and effective in the treatment of SUI.

They concluded, in pertinent part:

"The polypropylene midurethral sling has helped millions of women with SUI regain control of their lives by undergoing a simple outpatient procedure that allows them to return to daily life very quickly. With its acknowledged safety and efficacy it has created an environment

for a much larger number of women to have access to treatment. In the past, concerns over failure and invasiveness of surgery caused a substantial percent of incontinent women to live without treatment. . . .. This procedure is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our organizations which are dedicated to improving the lives of women with urinary incontinence."

In July 2014, the International Urogynecological Association, IUGA, issued a position statement on midurethral slings supporting their use to treat SUI in women. This statement concludes that: "There is robust evidence to support the use of MUS from over 2,000 publications making this treatment the most extensively reviewed and evaluated procedure for female stress urinary incontinence now in use. These scientific publications studied all types of patients, including those with co-morbidities such as prolapse, obesity, and other types of bladder dysfunction. It is, however, acknowledged that any operation can cause complications. For MUS, these include bleeding, damage to the bladder and bowel, voiding difficulty, tape exposure and pelvic pain; all of these may require repeat surgery but this is uncommon. Nevertheless, the results of a recent large multi-center trial have confirmed excellent outcomes and a low rate of complications to be expected after treatment with MUS. Additionally, long term effectiveness of up to 80% has been demonstrated in studies including one which has followed up a small group of patients for 17 years."

Most recently, in November 2015, ACOG and AUGS issued a Joint Practice Bulletin regarding Urinary Incontinence in Women. In particular, this Bulletin states, among other things, that:

The following conclusions and recommendations are based on good and consistent scientific evidence (Level A)….:

- Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparascopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings.
- There are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women.

I agree with and support each of these position statements. As a member of these medical societies, I am proud that we have the courage as a medical community to let our voices be heard to support the availability and appropriate use of mid-urethral slings such as Gynecare TVT and TVT Obturator.

Known Risks of All Incontinence Surgeries

There are several complications of any anti-incontinence surgery which are, through clinical experience and reporting in literature, well known to surgeons who routinely perform these procedures and are learned in the course of their training. These procedures carry a risk of damage to the surrounding nerves or vessels which can result in internal sphincter deficiency or hemorrhage. There is the possibility of retropubic bleeding; the space of Retzius or retropubic space is an area with a rich venous plexus which can be inadvertently disrupted causing significant bleeding which may be difficult to control. Injury to the lower urinary tract (ureter,

bladder or urethra) in the course of dissection has been reported. Bowel injury is a rare but reported complication.

Difficulty urinating from surgical overcorrection either from a sling or retropubic suspension may require additional surgery to release the obstruction. As is the case with other types of sling surgery, tensioning of a midurethral sling requires experience and understanding of the tension free technique. Adjusting the tension on a sling is one of the most critical parts of the procedure, with significant impact on its outcome. Placing the sling on too much tension can result in postoperative voiding complaints – de novo urgency, frequency, urinary retention and/or the need for a sling revision. Using too little tension may result in failure to cure stress incontinence. Moreover, different patients tolerate different amounts of sling tension. Some women may require a tighter sling to stay dry why others will be unable to tolerate any amount of direct tension. While there are understood general principles around tensioning, there is no specific set of 'rules' that will ensure the same results in every case. Often, it is more an art than an exact science, and the surgeon must rely on his or her training, experience and best judgment to determine how loose or tight to make a sling.

In addition, de novo urgency incontinence (UUI not present prior to surgery) and overactive bladder, wound complications, poor wound healing, and adhesions or scar formation are well described. Additional complications include infection (urinary tract and wound), pelvic pain and pain at the surgical site, and the formation of fistulas (holes that form from the urinary tract to the vagina causing continuous incontinence).

Painful intercourse or dyspareunia is a known but rare complication of any anti-incontinence procedure. In the Schimpf analysis, dyspareunia was reported at a rate of .99%,

0.16% and 0% for autologous fascial sling, obturator sling and retropubic synthetic sling respectively. In both the Cochrane review (Ford 2015) and the five year follow up on the TOMUS trial (Kenton 2015), sexual function was increased after the obturator sling insertion as compared to preoperative. Similar findings were reported by Filocamo et al. (J. Sex Med. 2011). Zyczynski et al. assessed the effects of midurethral sling surgery on sexual function in patients enrolled in the TOMUS trial at 2 year follow up. Mean sexual function scores improved significantly in both the transobturator sling group and the retropubic group, with no significant difference between the two. Furthermore, dyspareunia, coital incontinence, and fear of coital incontinence improved significantly after sling surgery. Zyczynski HM, et al: Sexual activity and function in women more than 2 years after midurethral sling placement. Am J Obstst Gynecol. 2012; 207(5): 421. Improved sexual function is related to a woman's sense of well-being. Incontinence is an embarrassing condition which may prevent a woman from engaging in intimate relationships which may induce leakage. Successful sling surgery is a liberating phenomenon for a sexually active previously incontinent female.

The risk of groin pain is unique to transobturator slings. In the immediate postoperative period, groin pain is the result of the pathway of the passers through the muscles of the inner thigh and groin (obturator internis, the adductor brevis, adductor magnus, and gracilis muscles) as well as the positioning of the patient in exaggerated lithotomy. In most cases, pain from muscle swelling will resolve in the first 24 to 48 hours and rarely lasts beyond 4 weeks. (Meschia, M et al Int Urogynecol J Pelvic Floor Dysfunct. 2007 Nov;18(11):1257-61). Long term or severe complications associated with trocar passage are rare. (Walters, M., Weber, A, Which sling for which SUI patient?, OBG Management, May 2012, Vol. 24, No. 5.)

A meta-analysis 17 of randomized controlled trials comparing retropubic with transobturator slings found that the odds ratio of groin/thigh pain was 8.3 for transobturator as compared to retropubic slings. (Latthe PM et al. BJOG. 2007;114:522-31). A French registry of TVT-O procedures involving 984 patients reported a 2.7% rate of residual pain lasting greater than 4 weeks duration. (Collinet P, et al Int Urogynecol J Pelvic Floor Dysfunct. 2008.) This is similar to what was reported by Richter et al. 2010, where post-operative pain greater than 6 weeks was noted in 2.0% of patients who had obturator slings and 2.3% of patients with retropubic slings. In the Schimpf meta-analysis (2014), groin pain was found to be highest in the obturator group: in the 17 RCTs reviewed, the reported summary of incidence was 6.5%, but this number includes both immediate and persistent pain. The Tommaselli (2015) medium and long term outcome analysis has a similar finding of 6% however the authors note that "all reported episodes, i.e. postoperative, persistent and chronic pain, are included in this analysis and most were postoperative or persistent pain that resolved within weeks or months, with no long-term sequelae. The rate of chronic pain in the groin and/or the thigh is far lower. It must be underlined that not all studies clearly defined postoperative, persistent and chronic pain, so that it was difficult to correctly identify the cases that remained unresolved."

Management of Mesh Exposures Following Sling Placement

In 2011, in order to standardize definitions, the International Continence Society (ICS) and International Urogynecologic Association (IUGA) created definitions for graft complications. The term "exposure" is defined as the presence of graft material in the wall of the vagina. An equivalent term is extrusion. In contrast, the term "perforation" or "erosion" implies that the graft has entered a visceral cavity such as the bowel or urinary tract. In the past the term erosion was used synonymously with exposure. True mesh erosion (into a visceral cavity) is

extremely rare (<1%). (Kuuva, et al Acta Obstet Gynecol Scand. 2002 Jan;81(1):72-7. A nationwide analysis of complications associated with the tension-free vaginal tape (TVT) procedure.)

Mesh exposure is a known complication of TVT and other types of synthetic midurethal slings with incidence in the literature typically between 0 to 7%. (AUA Guidelines Dmochowski, R., J. Urol. 2010; Schimpf et al. 2014.) Sometimes exposures happen due to technical error. The graft needs to be placed deeply under the vaginal wall in the true preurethral space without "splitting the fascia" in the dissection. Otherwise the tissue over the sling is too thin to promote adequate healing. Furthermore if there is a "buttonhole" or direct passage of the trocar through the vaginal wall, it needs to be recognized or the mesh will be placed directly into the vaginal cavity, usually through a lateral sulcus. Non-technical or patient factors for exposure include poorly controlled diabetes, steroid use, smoking history, multiple previous surgeries with significant scar tissue and age or decreased vaginal wall estrogenization. In these cases, the exposure is usually noted at the site of the vaginal incision. Sometimes the exposure occurs because the patient may have done something too strenuous in the immediate post-operative period, or returned to sexual activity too quickly, causing breakdown of the vaginal incision and subsequent mesh exposure. This is literally the case of "popping a stitch." Some authors have advocated that hematoma present under the vaginal wall contributes to poor wound healing and subsequent mesh exposure. (Frankman, EA Obstetrics and Gynecology International Volume 2013.) These factors are all relate to principles of wound healing and fall into the category of wound healing complications.

Although mesh exposure is not a complication seen in traditional surgeries that do not employ a sling, other types of graft materials used in sling surgery do present a risk of exposure.

Allografts and biologic materials have been shown to have equivalent rates of exposure to mesh (Drake et al, Urogyn J Pelvic Floor Dys. 2005; Flynn MK, AM J Obs Gyn, 2005). In most cases, allograft extrusions are managed non-surgically.

The management of mesh exposure is dependent on many different factors: the patient's age and comorbidities, the size and location of the exposure, the patient's symptoms and whether or not she is sexually active. Hammad et al. (Australasian survey, Eur. Urol. 2005) reported that 35% of vaginal erosions were asymptomatic and the exposure was discovered on routine follow-up. Kobashi et al. presented consistent data in a study of > 90 women who received a polypropylene mesh for the treatment of SUI; 3 developed vaginal exposure, but only 1 had symptoms such as pain or discomfort during sexual activity. (J. Urol. 2003;169:2242–3.) In my own practice, I have had similar findings.

While several authors have reported on their experience with mesh exposure, there is currently no evidence-based consensus on exactly how to manage exposures. That said, it is widely practiced and believed that, in general, small asymptomatic exposures can usually be successfully managed conservatively with pelvic rest and localized estrogen cream, or in-office excision. Larger and symptomatic exposures may require surgical excision (either partial or complete) to remove the exposed implant. Once adequate vaginal flaps have been created, the vaginal wall is closed with absorbable suture. In reviewing the literature the risk of reoperation after such a procedure for mesh extrusion is extremely low, although reoperation due to recurrent stress incontinence is documented. (Viereck et al., Int. Urogyn. J., 2013; Clifton et al., J. Urol. 191: 710–14, March 2014.)

Removal of mesh for the treatment of exposure is, in most cases, a successful practice and the risk of reoperation after such a procedure is low. This is further illustrated by the table set forth below:

META-ANALYSIS	NUMBER OF EVENTS/TOTAL PATIENTS TVT/TVT-O	EXPOSURE RATE TVT/TVT-O	REOPERATION RATE TVT/TVT-O
Ford 2015	21/1000/ 24/1000	1.5/0.4%	1.6-2.4%/.8-2.2%
Tommaselli 2015	3801/1375	2.1%/2.7%	
Schimpf 2014	84/5684	1.4%	1.9% (for exposure) (13/703 patients)/2.7 (14/518 patients)
Ogah 2011	2/153 and 8/249	1.3%-3%	1.6% - 2.4% (related to tape insertion or postop voiding dysfunction)/ 0.8--2.2%
Novara 2008	4764 (Table 6)	1.1% overall	3.2% overall

Overall, the reliable scientific literature demonstrates that the rates of reoperation after TVT are in the low single digit range. (Welk B. et al., *Removal or Revision of Vaginal Mesh Used for the Treatment of Stress Urinary Incontinence*, JAMA Surg. 2015 Sep; 9:1-9; Unger CA et al., *Indications and risk factors for midurethral sling revision*, Int. Urogyn. J. 2015 Jul 2. [Epub ahead of print] PubMed PMID: 26134541; Jonsson Funk M, et al., *Sling revision/removal for mesh erosion and urinary retention: long-term risk and predictors*, Am J Obstet Gynecol. 2013 Jan; 208(1):73.e1-7; Schimpf et al., Society of Gynecologic Surgeons Systematic Review Group. *Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis*. Am J Obstet Gynecol. 2014 Jul; 211(1):71.e1-71; Laurikainen E. et al., *Five-year*

results of a randomized trial comparing retropubic and transobturator midurethral slings for stress incontinence. Eur Urol. 2014 Jun;65(6):1109-14; Serati M, et al., *Tension-free vaginal tape for the treatment of urodynamic stress incontinence: efficacy and adverse effects at 10-year follow-up*. Eur Urol. 2012 May;61(5):939-46; Nguyen JN, et al., *Perioperative complications and reoperations after incontinence and prolapse surgeries using prosthetic implants*. Obstet Gynecol. 2012 Mar;119(3):539-46; Novara G, et al., *Complication rates of tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials comparing tension-free midurethral tapes to other surgical procedures and different devices*. Eur. Urol. 2008 Feb;53(2):288-308.) This is also consistent with the extensive experience I have had with midurethral slings in my practice and training.

Material Properties of Synthetic Mesh

Synthetic meshes have different properties. They can be absorbable or non-absorbable. Absorbable meshes are tolerated well in the body but have the disadvantage of less tensile strength. Furthermore, the scar tissue which forms when they dissolve is not as strong as the reinforced tissue, making them less desirable for use in stress incontinence surgery. Mesh can be microporous <10μm or macroporous >75μm. (Amid, PK Classification of biomaterials and there related complications in abdominal wall hernia surgery. Hernia, 1997). It can be monofilament or multifilament. A mesh pore size of 75μm or greater is necessary to allow macrophages and fibroblasts to enter freely to eradicate bacteria (White, TA ASAIO J.,1988). Lastly, multifilament (braided) have small interstices that are more likely to promote infection than monofilament meshes.

TVT and TVTO slings are made of PROLENE mesh, which is type 1 non-absorbable synthetic mesh – it is macroporous (1.5 mm) and monofilament (polypropylene) making it an excellent sling material. (Gomelsky A, Dmochowski R., J. Urol. 178:4, 1171–1181, October 2007.) Based on my clinical experience and review of the clinical experience of numerous others as reflected in the peer reviewed medical literature, the pore size of PROLENE mesh is entirely appropriate to promote healthy tissue integration. If it were not, we would be seeing failure, rejection and complications on a far grander scale. In fact, the AUGS/SUFU January 2014 Position Statement referenced above cites the Nilsson 17-year TVT data (using the same mesh construction as TVTO) for the proposition that "As a knitted implant for the surgical treatment of SUI, macroporous, monofilament light-weight polypropylene has demonstrated long term durability, safety and efficacy up to 17 years." The question of whether the pore size changes after implantation is also of no clinical significance. PROLENE mesh does not demonstrate a higher rate of infection or extrusion than any other implanted material, which would be a consequence of deceased pore size or microporous mesh were it to have a clinical impact.

In fact, one of the advantages of PROLENE mesh is its low infection rate. Although infection is a known risk when using any implant, the medical literature on polypropylene mid-urethral slings shows an extremely low rate of infection. In fact, the large meta-analyses report little to no infection with synthetic mid-urethral slings. (Ogah et al. (2011)); Dmochowski, R., J Urol. 2010; Schimpf et al. 2014).) That is very consistent with my personal experience in my practice; I rarely if ever have to treat my patients postoperatively with antibiotics to treat a sling infection. Urinary tract infections may develop postoperatively, but not with any greater degree than traditional repairs as evidenced in the TOMUS and SISTre trials. Explanted meshes are by

definition "infected" if they have been exposed to the vaginal milieu. But even this situation has questionable clinical significance as patients with PROLENE mesh exposures do not mount a classic "infection" response such as fever or purulent drainage. In any event, the IFUs for TVT and TVTO explicitly warn surgeons of the risk of infection potentiation, inflammation, and extrusion, which would be the indicators that a mesh is being rejected by the patient.

Plaintiffs' experts offer several opinions regarding so-called particle loss and fraying of mechanical cut mesh, degradation, chronic foreign body reaction, excessive contraction, roping, curling and other issues that they contend make PROLENE® mesh used in mechanically cut TVTO unsuitable to treat SUI in women. As a clinician with experience placing over 1500 slings, the overwhelming majority of which are Gynecare mesh slings, treating patients post-operatively, and based on my review of medical literature and training, I must disagree. My experience and the experience of countless other surgeons as reflected the wide body of medical literature on TVT and other polypropylene mid-urethral slings do not suggest that these factors, if they exist, manifest in clinical significance for patients, and certainly not on any widespread basis. If they did, we would not see the levels of safety and effectiveness in TVT brand slings in the medical literature that make them the procedure of choice for myself and so many of my colleagues.

Regarding claims of "particle loss" and "fraying" with mechanical cut mesh, I have searched the medical literature on this point and have found no evidence whatsoever to suggest that slings using laser cut mesh are safer than slings using mechanical cut mesh, or vice versa. Whether to use mechanical cut mesh or laser cut mesh is solely a matter of surgeon preference, and Ethicon appropriately offers both versions to meet that surgeon preference. I have used TVT implants cut in both ways and do not note any difference in application.

Furthermore, the overall extensive body of clinical data for Gynecare TVT brand products does not support the conclusion that PROLENE® mesh degrades in the body in any manner that has a clinical impact on patients. Clavé et al. (2010) studied how polypropylene mesh which was explanted due to erosion or infection was altered from its pre-implant state. The authors used histologic, chemical analysis, infrared spectroscopy and differential scanning calorimetry. Monofilament polypropylene products had less surface cracking (which they reported was degradation) than multifilament products. Clavé et al. noted that despite exhaustive testing, they could not explain their findings. They stated, "Several hypotheses concerning the degradation of the PP are described. None of these, particularly direct oxidation, could be confirmed in this study." The authors conceded that a weakness of the study was that there was no opportunity to compare explanted mesh from uncomplicated procedures with explanted mesh from the complicated procedures which makes it difficult to conclude if there would also be alterations in products which had not eroded or become infected. Given these limitations recognized even by the study's authors, it cannot be concluded to a reasonable degree of medical certainty or probability that mesh degradation happens in a clinically significant way. This issue has also been evaluated by medical societies AUGS and SUFU which have concluded that the clinical data do not support the extrapolation of reported "surface cracking" in a minority of the Clave samples to degradation. (AUGS-SUFU Frequently Asked Questions by Providers: Mid-urethral slings for Stress Urinary Incontinence. March 2014).

Alternatively, Woodruff et al. (2008) performed histopathologic analysis on 24 explants at 2-34 months after implantation. The indications for removal were not mesh exposure or infection but rather a lack of sling efficacy in 2, urinary retention in 9, and sling obstruction in 13. The types of graft materials were polypropylene mesh (PPM) in 10, autologous fascia in 5,

porcine dermis in 4, cadaveric dermis in 3, and cadaveric fascia in 2. No graft degradation had occurred in PPM material. Interestingly, autologous and cadaveric fascia had the most demonstrable graft degradation. The fact that numerous studies on TVT have proven its durability and safety for many years post implant does not support short or long term degradation. If it did degrade in a clinically significant way, surgeons would see far lower levels of durability in their TVT and TVT-O repairs, and that is certainly not something that I have seen in my clinical practice over many years, nor is that consistent with the reliable scientific studies in women implanted with TVT. Nor does the notion that PROLENE® degrades in the human body make sense given that PROLENE® sutures have been successfully used in vaginal surgery for decades.

The medical literature also does not provide evidence that the use of PROLENE mesh results in excessive contraction of tissues causing complications to the patient. To the contrary, Dietz et al. report that based upon ultrasound imaging, the TVT does not seem to contract or shorten over a median observation period of 1.6 years: "Over the observed period between 6 weeks and 3.3 years after TVT placement, our data do not provide any evidence for contraction or shortening of the TVT." Dietz et al., Am. J. Obstet. Gynecol. 2003, 188:950-953. Similarly, in the 17 year follow up performed by Nilsson et al. (2013), the authors reported that there seemed to be no shrinkage of the TVT mesh over time.

Finally, in my experience of over 1500 mesh slings, I have not seen a sling rope or curl in the human body unless an unnecessary amount of tension is placed on the implant causing it to deform. The IFUs for TVT and TVTO are clear in stating that the tape should be placed at the midurethra without tension, and that surgeons should be trained in implanting the devices before using them.

Alternative Meshes

Based on my experience and my review of the medical literature, I am not aware of any design or material of mid-urethral sling that does not pose the potential risks of the TVT device, including the risk of exposure, which may require revision. Nor am I aware of any surgery to treat SUI that does not come with a possible risk of urge incontinence, urgency, frequency, or corrective surgery that would create additional scarring.

The medical literature shows a risk of exposure from the use of any sling, and the risk of wound complications from any surgery to treat SUI, some of which will require surgical treatment. (Dmochowski RR, et al., Female Stress Urinary Incontinence Update Panel of the American Urological Association Education and Research, Inc, Whetter LE. Update of AUA guideline on the surgical management of female stress urinary incontinence. J Urol. 2010 May;183(5):1906-14; revised 2012 https://www.auanet.org/common/pdf/education/clinical-guidance/Incontinence.pdf; Schimpf et al., Society of Gynecologic Surgeons Systematic Review Group. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014 Jul;211(1):71.e1-71.e27.) Still, the reoperation rates in the large systematic reviews such as Ford (1.6% to 2.4%) and Schimpf (1.9%) are acceptably low. The macroporous TVT PROLENE polypropylene mesh is the most studied mesh in the world for the surgical treatment of SUI and has the highest degree of biocompatibility when used in the application. (Ford 2015; AUGS-SUFU Frequently Asked Questions by Providers: Mid-urethral slings for Stress Urinary Incontinence. March 2014; Ogah J, Cody DJ, Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane review. Neurourol Urodyn. 2011 Mar;30(3):284-91.)

Alternative meshes such as GYNEMESH PS and ULTRAPRO have not been studied nearly to the extent as TVT for the treatment of SUI. Unlike TVT, they are not recommended as a treatment of SUI by the pertinent medical societies. I have not found credible evidence in the medical literature that the use of GYNEMESN PS, ULTRAPRO, or laser cut PROLENE Mesh, eliminates (or even reduces) the possible risks of exposure, the need for revisions, or the risk of postoperative incontinence or voiding symptoms. In Okulu 2013, the rate of exposure with GYNEMESH PS and ULTRAPRO was equivalent to or greater than the exposure rates typically reported for TVT PROLENE mesh, and was based on a small patient groups. (Okulu 2013; see Novara 2008, Table 6, listing several TVT studies with 24 month follow listing vaginal exposure rates between 1 and 2%.) The Okulu article also involved a different surgical procedure, different shape of mesh, and TVT PROLENE mesh was not a comparator. (Okulu 2013.) Also, when GYNEMESH PS and ULTRAPRO are used in a different vaginal indication, to treat prolapse, they do carry risks of exposure and dyspareunia. (See Milani 2012, reporting 14.8% exposure and 9% dyspareunia following use of ULTRAPRO to treat prolapse.)

TVT/TVT-O Warnings

The TVT and TVT-O IFUs and the TVT Surgeon's Resource Monograph appropriately reflect the potential risks associated with the use of the devices as they are reported in the peer reviewed medical literature which I have researched and considered in preparing this report. This opinion is based on numerous factors:

1. The extensive medical literature that has studied TVT in thousands of patients over the past 20 years, including Level 1 meta-analyses and randomized controlled trials, as well as numerous prospective studies following patients for over ten years. These studies are

discussed in detail in my TVT general report served in this MDL proceeding. My detailed review of that literature leads me to the conclusion that the TVT IFU and professional education materials such as the TVT Surgeon's Resource Monograph adequately warn of the product's potential risks because they reflect the potential risks that are reported in the peer reviewed medical literature. I have also reviewed and considered the FDA's "Blue Book Memo" which provides guidance on device labeling, and Ethicon's Standard Operating Procedure on Labeling (HMESH_ETH_11642462), but these sources are not as important to me as the peer reviewed medical literature in assessing the potential risks of TVT. While labeling guidance documents from the FDA and the company provide general information on the goals of labeling, the medical literature provides detailed information on what adverse events have actually been demonstrated in thousands of women tracked over time, some of them for several years.

2. My extensive surgical experience in implanting approximately 1500 slings, as well as treating patients who were implanted by other doctors.

3. My years of experience in training residents and fellows in how to perform sling procedures. For the past 8 years I have been associate fellowship director of an ACGME-approved FPMRS fellowship program. I have a systematic approach to teaching fellows to safely place TVT by reviewing the instructions for use with them, having them watch me place TVT and ultimately supervising their performance in placing TVT on their own. This process equips me to evaluate the adequacy of the IFU because I have an understanding of what a new user needs to know in order to safely and effectively perform the procedure. I have reviewed the IFUs for TVT-O and TVT-Exact with my fellows as part of their training on the devices.

4. My attendance at numerous medical conferences, including the Annual Meetings of medical societies such as AUGS and SUFU, where I have observed numerous presentations of

TVT and TVT-O data in the hands of many different surgeons who have presented their findings in oral presentations, posters and abstracts.

5. My training as a urology resident and as a Fellow in Female Urology and Voiding Dysfunction at the New York University School of Medicine, where I was trained to perform TVT and other pelvic surgeries by Dr. Vic Nitti.

The TVT and TVT-O IFUs clearly and adequately state indications, contraindications, surgical steps, warnings and precautions and adverse reactions associated with the use of TVT and TVT-O. The first paragraph of the IFUs states that it is not intended to be a comprehensive reference to surgical technique to treat SUI, and that the device should be used only by physicians trained in the surgical treatment of SUI and trained in the use of the device itself. This is very important because it conveys that Ethicon expects that the users of TVT and TVT-O will be a trained pelvic floor surgeons with a base knowledge of pelvic floor anatomy and risks of pelvic floor surgery in general. The IFUs repeat the warning about proper training on the device in the "WARNINGS AND PRECAUTIONS" section of the IFU. That section further advises physicians to avoid large vessels, nerves, bladder and bowel, and that "attention to patient anatomy and correct passage of the device will minimize risks." It also reinforces the instructions for the surgical placement of the device in emphasizing: "Ensure that the tape is placed with no tension under the mid-urethra." As discussed above, the WARNINGS AND PRECAUTIONS section also warns of the possible risk of de novo detrusor instability which leads to overactive bladder, urgency and frequency symptoms, as well as (in the case of TVT-O) transient leg pain.

The Adverse Reactions section of the IFUs is appropriate because it correctly reflects the potential complications that are reported in the most reliable medical literature --- meta-analyses,

RCTs, and long and medium term prospective observational trials – which are discussed in detail above in my report. It also properly warns doctors of the potential implications of over-tensioning, namely obstruction of the lower urinary tract. The Adverse Reactions section provides:

- Punctures or lacerations of vessels, nerves, bladder, urethra, or bowel may occur during needle passage and may require surgical repair.
- Transitory local irritation at the wound site and a transitory foreign body reaction may occur. This response could result in extrusion, erosion, fistula formation or inflammation.
- As with all foreign bodies, PROLENE mesh may potentiate an existing infection. The plastic sheaths initially covering the PROLENE mesh are designed to minimize the risk of contamination.
- Over-correction, i.e. too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction.

(TVT and TVT-O IFUs).

It is my opinion that because the vast body of medical literature does not demonstrate the cytotoxicity, degradation, chronic inflammation leading to complications and other negative consequences that plaintiffs' experts allege, these claimed effects do not need to be warned about in the IFU. Also, while dyspareunia and pelvic pain are known potential risks of any surgery in the pelvic floor, the medical literature does not reflect that such symptoms typically are associated with TVT or TVT-O in absence of surgical error in placement, over-tensioning, exposure (which is warned about), and concomitant surgeries.

I have also reviewed the 2015 revisions to the TVT and TVT-O IFUs and note that while they use additional language and descriptions to describe potential risks, or re-state the risks that were previously warned about, they do not provide information that is new to the medical

community. Much of the added language relates to general risks of pelvic floor surgery that are not a function of the device (for example, that there may be pain or urinary symptoms), or that are obvious to a trained pelvic floor surgeon (for example, that the device may not work, or may require additional surgeries to treat complications).

The TVT Surgeon's Resource Monograph supplements the warnings discussions in the TVT and TVT-O IFUs. It is a booklet that was issued in 2001 and compiles the advice and best practices of a panel of 17 surgeons who were very experienced in TVT at that time. It provides detailed guidance on patient preparation, anesthesia, incisions, device placement and post operative care. It also provides paragraphs of discussion on numerous potential adverse events including vaginal bleeding, retropubic hematoma, vaginal perforation, difficulty placing the needle, bladder perforations, voiding dysfunction and retention, injured urethra, urethral erosion, mesh protrusion or defective healing, vascular injuries, bowel perforations, de novo urge incontinence, infection of the mesh, urinary tract infection and device failure.

In addition, I have reviewed Ethicon's patient brochures for the TVT family of products. For the same reasons as discussed above with the IFUs and professional education materials, find them to be appropriate for the limited role of a patient brochure. They are comprehensive in their discussion of the disease state of SUI, treatment options and potential risks. The risk discussion mirrors the IFU and is not misleading. While the patient brochure does not list every possible risk that a patient could encounter in surgery, that is not the role of a patient brochure. Rather, it is the role of the patient's physician to engage the patient in a comprehensive risk discussion that is tailored to the patient's individual presentation and medical history.

Summary of Opinions

For the reasons set forth above, it is my opinion to a reasonable degree of medical certainty that:

1. Gynecare TVT and TVT-O are safe and effective products that are supported by a substantial amount of clinical data over 20 years, including the data supporting Gynecare TVT Retropubic, which employs the same mesh implant. They are indeed the "gold standard" in the treatment of SUI, and an appropriate treatment option for many women who suffer with this difficult and embarrassing condition.

2. The benefits of TVT and TVT-O far outweigh the risks in a patient who is a proper candidate for surgery, and they are not defectively designed. My opinion on this is based on: 1) the performance of these products in these clinical studies which I have reviewed – Level 1 meta-analyses, RCTs and long term prospective studies studying thousands of women over 20 years; 2) my extensive surgical experience implanting these slings and treating women who have been implanted with them; and 3) my experience advising Ethicon [and other companies] on products in development, as detailed above.

3. The PROLENE® mesh tape used in TVT and TVT-O is an appropriate, effective and safe material for use in this indication. Polypropylene mesh and sutures have been used an implant for decades. Based on my review of the peer-reviewed medical literature and my surgical experience implanting these devices and treating patients who have had them implanted, the pore size of the mesh tape in TVT and TVT-O is sufficiently large to allow for proper tissue ingrowth, and has not presented risks of infection, particularly in relation to other implants.

4. The overall and extensive body of clinical data for Gynecare TVT and TVT-O does not support the conclusion that PROLENE® mesh degrades in the body in any manner that has a clinical impact on patients. If it did degrade in a clinically significant way, surgeons would see far lower levels of durability in their repairs, and that is certainly not something that I have seen in the peer reviewed medical literature or my clinical practice over many years.

5. The safety and efficacy of PROLENE® mesh as an SUI sling does not depend on whether it is mechanically or laser cut. Whether to use mechanically cut or laser cut mesh tapes is a matter of surgeon preference and for that reason, it is appropriate that Ethicon sells both options. There is no clinical evidence in the medical literature that particle loss, to the extent that it occurs with mechanically cut mesh, has any clinical significance to the patient. There is also no body of clinical evidence demonstrating that laser cut mesh have a better safety profile for the patient than mechanical cut PROLENE® mesh to treat SUI.

6. There is no credible evidence in the medical literature of an alternative mesh material that, when used to treat SUI, reduces or eliminates the potential risks of PROLENE®.

7. A foreign body/inflammatory response is an expected and desired physiological outcome of the placement of any surgical implant. The peer reviewed medical literature I have reviewed does not support the notion that this response has any negative impact on clinical outcomes when the TVT-O is placed correctly.

8. The possible risks of TVT and TVT-O are adequately described in their Instructions for Use, the patient brochures for the TVT family of products, and in Ethicon's professional education materials. The IFU and the professional education materials also

appropriately take into account the foundational level knowledge of the trained surgeon who is using the product, as is specifically stated in the IFUs.

Expert Rates

My work on this matter has been or will be billed as follows: $500 per hour for records review, preparation of Expert Reports, and consultation; $4000 per half day of deposition or trial testimony; and $7500 for full day of deposition or trial testimony.

Consulting with Ethicon

Based on Ethicon's records, I have preceptored about five events for Ethicon between 2008 and 2011, in which I trained other doctors in the safe and effective use of Prolift and TVT products. For my services, I was compensated a total of approximately $10,000.

Dated: June 6, 2016

NICOLE B. FLEISCHMANN, M.D.

EXHIBIT B TO REPORT OF NICOLE B. FLEISCHMANN, MD

List of Materials Reviewed

Updated August 6, 2016

Company Documents:

1. 1998 TVT Professional Education Program Speaker's Guide Slide Deck [ETH.MESH.05795537-99]

2. 2001 Slides from Paul Parisi binder - Gynecare TVT Tension-free Support for Incontinence Professional Education Slides [ETH.MESH.05795421-508]

3. 2002 Dr. Miklos Presentation Slides Minimizing & Managing Intraoperative Complications: TVT Sling [ETH.MESH.00397674]

4. 2002 TVT Advanced Users Forum Presentation Slides: Gynecare TVT Tension-free Support for Incontinence [ETH.MESH.08156958]

5. 2003 - Gynecare TVT: Tension-free Support for Incontinence General Professional Education Presentation Slides [ETH.MESH.00373310-88]

6. 2006 - TVT-O Summit Presentation Slides by Raders and Lucente [ETH.MESH.00993273]

7. 2007 Pelvic Floor Summit Agenda [ETH.MESH. 02109874-75]

8. 2008 Pelvic Floor Summit Agenda [ETH.MESH. 00819498-99]

9. 2008 - Treatment of SUI with the Gynecare TVT Family of Products Presentation Slides [ETH.MESH.00369995]

10. 2008.12.10 TVT Patient Brochure

11. 2009 - The Science of 'What's Left Behind…' Evidence & Follow-Up of Mesh Use for SUI by Dr. Doug Grier [ETH.MESH.03751819]

12. 2010 - Gynecare TVT Exact Professional Education Presentation Slides [ETH.MESH.00295355]

13. 2012 - Gynecare TVT Exact Continence System Professional Education Presentation Slides-Updated [ETH.MESH.08117473]

14. 2013 - Clinical Expertise Tension-free Midurethral Sling: Market Update Presentation Slides-Prof Ed [ETH.MESH.10281860]

15. 2015 TVT IFU

16. 2015 TVT Patient Brochure

17. TVT 'Stop Coping…' Patient Brochure – [ETH.MESH.06087471-72]

18. Gynecare TVT…SUI affects 1 in 3 women… Patient Brochure – [ETH.MESH.06087513-14]

19. 'Stop Coping…' Gynecare TVT Patient Brochure – [ETH.MESH.08003295-302]

20. 'Stop Coping…' Gynecare TVT Patient Brochure – [ETH.MESH.08003303-18]

21. Corbet-IFU- 17-In Use From 11/29/10 to Present [ETH.MESH.03427878-946]

22. Gynecare TVT Tension-free Support for Incontinence Advanced Users Forum for the Experienced Clinician Presentation Slides [ETH.MESH.10220659]

23. Gynecare TVT Tension-free Support for Incontinence Professional Education Presentation Slides [ETH.MESH.08107354]

24. The History of TVT [ETH.MESH.03932912-914]

25. TVT IFU In Use From 10/13/08 to 11/22/10 [ETH.MESH.2340504-567]

26. TVT IFU In Use From 11/29/10 to Present [ETH.MESH.3427878-946]

27. TVT IFU 2008 [ETH.MESH.05222687]

28. 01/28/98 Letter from FDA re: K974098 TVT System [ETH.MESH.371496-594]

29. 11/11/10 Letter from John Young re: Global Regulatory Strategy for TVT IFU (RMC P15506/E) Update (Part II, RA0001-2010, Rev. 1) [ETH.MESH.341006-11]

30. Patient Brochure: "Stop coping, start living." [ETH.MESH.8003303-17]

31. Patient Brochure: "Stop coping, start living." [ETH.MESH.8003295-301]

32. Surgeon's Resource Monograph, A Report of the June 2000 Summit Meeting [ETH.MESH.658177-658198]

33. TVT Surgeons Resource Monograph - June 2000 [ETH.MESH.10027307-28]

34. TVT Surgeons Resource Monograph copy review form [ETH.MESH.00161387-89]

35. Clinical Evaluation Report, Gynecare TVT Tension-free Vaginal Tape / Tension-freeVaginal Tape Accessory Abdominal Guide [ETH.MESH.4384126-65]

36. 09/07/2009 Safety review: TVT and TVT-O procedures [ETH.MESH.1751069-94]

37. Clinical Expert Report [ETH.MESH.1784823-28]

38. Email re: Performance Evaluation of TVT Prolene Blue Mesh [ETH.MESH.6696411-19]

39. Letter from Dr. Joerg L. Holste, re: Biocompatibility Risk Assessment for Laser-cut Implant of Gynecare TVT

40. Letter to Weisberg/Robinson re: Elongation Characteristics of Laster Cut PROLENE Mesh for TVT, from Kammerer [ETH.MESH.1222075-79]

41. Email from Seppa re: Performance Evaluation of TVT U PROLENE Mesh: Mechanical vs. Laser Cut. Study (LIMS #BE-2004-1920) Version 2

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Expert Reports:

1. Blaivas, Jerry
2. Ducheyne, Paul
3. Elliot, Daniel (& materials cited in footnotes of Mullins expert report)
4. Iakovlev, Vladimir
5. Jordi, Howard
6. Kenton, Kimberly
7. Klinge, Uwe
8. Kohli, Neeraj (& materials cited in report)
9. Muehl, Thomas
10. Pence, Peggy
11. Rosenzweig, Bruce (& materials cited in footnotes of Mullins expert report)
12. Toglia, Marc

Deposition Transcripts & Exhibits:

1. Blaivas, Jerry
2. Elliot, Daniel
3. Hinoul, Piet
4. Iakovlev, Dr. Vladimir
5. Nager, Charles
6. Rosenzweig, Bruce
7. Toglia, Marc
8. Weisberg, Martin

I have also reviewed all materials or articles cited in my expert report, or supplements thereto, which are not included in this Exhibit B.